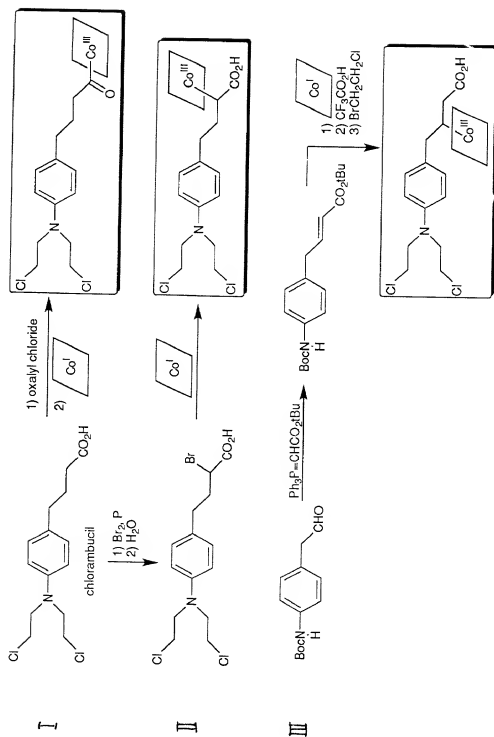


5



An etoposide-containing bioconjugate can be synthesized by the following method. Etoposide is a semisynthetic derivative of the natural product epipodophyllotoxin that is widely used against a variety of tumors, especially small cell lung carcinoma and germ cell tumors (De Jong et al., 1995). It has also shown considerable promise in the treatment of refractory cases of ovarian and breast cancer. Etoposide appears to function as a topoisomerase II poison.

Etoposide is conjugated to cobalamin, Co[SALEN] and other organocobalt complexes according to the following reaction schemes. Bioconjugates **8a** and **8b** require conversion of the free phenol of etoposide (**3**) to the corresponding chloroformate **17**. Direct acylation with Co(I) gives acylCo(III) derivative **8a**, while treatment with the previously described hydroxyethylCo(III) derivative **18** furnishes carbonate **8b**. This derivative is also available via acylation of **3** with the chloroformate **19** derived from **18**. Preparation of acetal-modified conjugate **8c** may be more challenging. The ethylene acetal of **3** can be hydrolyzed and then the acetal reformed using aldehyde **20a** or dimethyl acetal **20b** (Keller-Jusl et al., 1971). Compound **20a** may also be accessed via careful, selective oxidation of **18**, while **20b** should be available via alkylation of the Co(I) derivative with commercially available bromoacetaldehyde dimethyl acetal. In addition, the acetal of glucose can be formed and then the secondary alcohol of **21** can be glucosylated. Cleavage of **8a** or **8b** either give **3** directly via fragmentative pathways, or furnish products which can undergo eventual hydrolysis to **3**. Trapping with H• following homolysis of **8c** would then furnish **3**.